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Role of Noninvasive Hemoglobin Monitoring in Trauma

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14. ABSTRACT

Monitoring for acute blood loss is critical in surgical patients, and delays in identifying hemorrhage can result in poor outcomes. The current standard of care for monitoring patients at risk for bleeding is serial measurement of hemoglobin (Hgb) by standard laboratory complete blood count. Point-of-care testing (i.e., iSTAT®) can be a rapid method of evaluating Hgb, and spectrophotometry-based devices (i.e., Radical-7®) offer the advantages of being continuous and noninvasive. We sought to evaluate the accuracy of Radical-7® and iSTAT in measuring Hgb and assessing for blood loss when compared to gold standard complete blood count.

15. SUBJECT TERMS
Hemoglobin, hemorrhage, point of care testing, noninvasive

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1.0 SUMMARY

Radical-7® continuous hemoglobin measurement differs by more than ± 1.0 g/dL from gold standard automated laboratory hemoglobin measurements with a wide confidence interval in patients at risk for hemorrhage. Furthermore, concordance with complete blood count hemoglobin changes only occurred in 60% of cases, and continuous hemoglobin measurements could not be obtained 15% of the time. These findings limit the utility of noninvasive hemoglobin monitoring in detecting ongoing hemorrhage. In contrast, the iSTAT® point-of-care device was more accurate, had better correlation with laboratory values, and may be more useful as a method of assessing for acute blood loss in critically ill patients.

2.0 INTRODUCTION

Acute anemia and bleeding are major causes of morbidity and mortality in both surgical and nonsurgical patients. Hemorrhage in the intensive care unit (ICU) can be difficult to detect, and delays in identifying hemorrhage can result in poor patient outcomes. The current standard of care for monitoring patients at risk for bleeding is serial measurement of hemoglobin levels. At present, the photometric cyanmethemoglobin method is the most widely used technique for monitoring hemoglobin in the laboratory and is currently the gold standard for the measurement of hemoglobin concentration, as defined by the International Committee for Standardization in Hematology [1,2]. In addition to its reliability, laboratory analysis with complete blood count (CBC) can provide additional diagnostic information, such as platelet count, which can be useful when attempting to achieve hemostasis in the bleeding patient. However, this multistep process has potential for delay before final results are obtained. The time required for blood sampling, transport to the laboratory, analysis of the sample, verification of results, data entry, and retrieval of the actual lab value can delay receipt of these critical data from minutes to hours. Repeated sample collection can also result in a gradual hemodilution with progressive anemia, which may contribute to end organ injury and morbidity.

Immediate hemoglobin measurements are available with portable point-of-care devices, which utilize an extremely small quantity of blood (10 µL) for analysis. These devices can produce a measurement of hemoglobin concentration in less than 1 minute, making this potentially advantageous when timing of results is critical. Although use of point-of-care testing has become common in emergency departments, neonatal units, and operating rooms [3-5], it is invasive, and the accuracy of these devices has been reported to vary with hemoglobin level, potentially rendering this modality less accurate in detecting blood loss when compared with the gold standard of laboratory analysis.

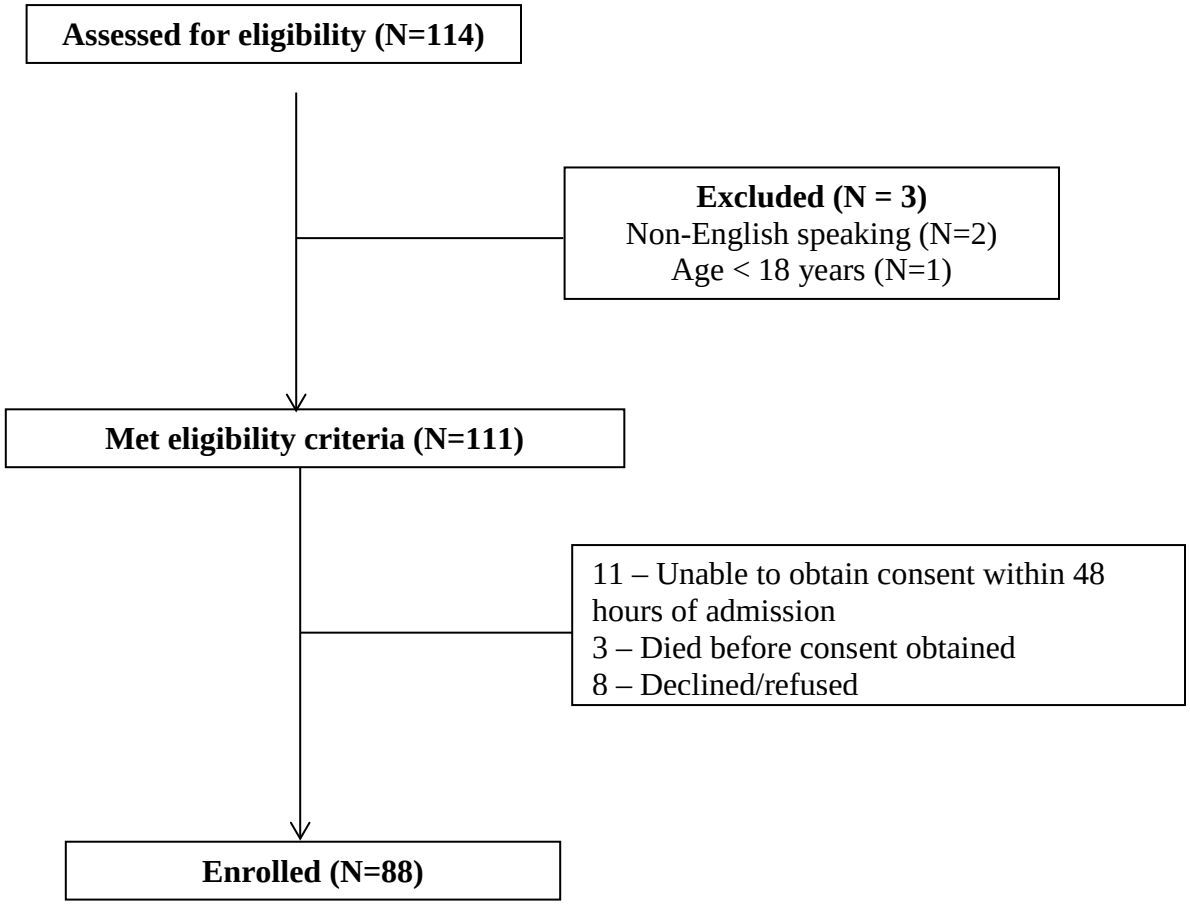
Recently, a noninvasive, spectrophotometry-based monitoring technology (Radical-7® Pulse CO-Oximeter; Masimo Corp., Irvine, CA) that provides continuous hemoglobin measurement (SpHb) has been developed. This technology measures the differential optical density of wavelengths of light passed through the finger in a method similar to conventional pulse oximetry. Transmitted light is captured by photodiode receptor and analyzed to create an analog signal that, in turn, is converted to a digital signal. While the accuracy and potential utility of noninvasive hemoglobin measurements using various devices have been previously described [6-9], only a few studies have examined its application to patients with the potential for bleeding with mixed results [10-14]. If these noninvasive methods of hemoglobin measurement can be validated in patients at risk for ongoing hemorrhage, use of this technology

may result in earlier detection of ongoing hemorrhage, expedite appropriate resuscitation, and improve patient outcomes.

The specific aim of this prospective cohort study was to compare the accuracy of noninvasive hemoglobin measurement (Radical-7®) and point-of-care testing (iSTAT®; Abbott Point of Care, Princeton, NJ) to invasive hemoglobin monitoring (standard laboratory evaluation) in patients at risk for blood loss.

3.0 METHODS

Adult patients (>18 years of age) admitted to the surgical ICU of a tertiary referral, Level I, American College of Surgeons verified trauma center with potential for hemorrhage were eligible for the study. Exclusion criteria included incarcerated individuals and patients unable to utilize a pulse oximetry device (i.e., extremity amputation, burns). Consent for participation was obtained directly for participating patients. In cases where the patient was not able to provide consent, the legally authorized representative or next of kin was utilized. The study was approved by the Institutional Review Board of the University of Cincinnati and was registered in ClinicalTrials.gov with ID NCT01709786 (see CONSORT diagram, Figure 1).



Serial CBC laboratory measurements were ordered based on clinical indications and performed on a Beckman Coulter LH780 hematology analyzer (Beckman Coulter, Brea, CA). As soon as a subject was eligible for the study, the Radical-7® noninvasive oximeter was attached to a finger from either hand via a non-disposable sensor. The sensor was placed on the first or second digit on the hand opposite the clinical pulse oximeter sensor whenever possible. If the need arose to place the Radical-7® probe on the same hand as the clinical oximeter sensor, the Radical-7® was shielded with a light-impermeable cover so as to prevent "cross talk" between the two sensors. Data from the oximeter were continuously recorded to the device and downloaded for later analysis. No data were collected from a subject's medical record until consent had been obtained. Each time the CBC was drawn, hemoglobin was also measured using point-of-care testing (iSTAT®). Additional data collected included patient demographics, use of vasopressors, arterial oxygen saturation (SpO2), and blood product transfusions. As SpHb may be affected by jaundice [14], bilirubin was recorded when available.

The accuracy of SpHb measurement can also be affected by the perfusion at the site of the probe. The perfusion index (PI) provides a relative numeric indication of the pulse strength at the monitoring site. PI values greater than 1.00 are desired [14]. Subset analysis of SpHb was performed on points with $PI \geq 0.5$ and $PI \geq 1.00$.

Results are expressed as mean ± standard deviation. The Bland-Altman technique with correction for multiple measurements was used to compare the hemoglobin measurements obtained from the iSTAT® and Radical-7® devices to the hemoglobin measurement from the CBC [15]. CBC hemoglobin was considered the gold standard, with accuracy defined as ±1.0 g/dL.

To examine if serial hemoglobin measurements obtained by iSTAT® and Radical-7® changed in the same direction (increased vs. decreased) as the CBC hemoglobin, concordance measurements for paired temporal differences were performed with calculations of McNemar statistic used to test for agreement.

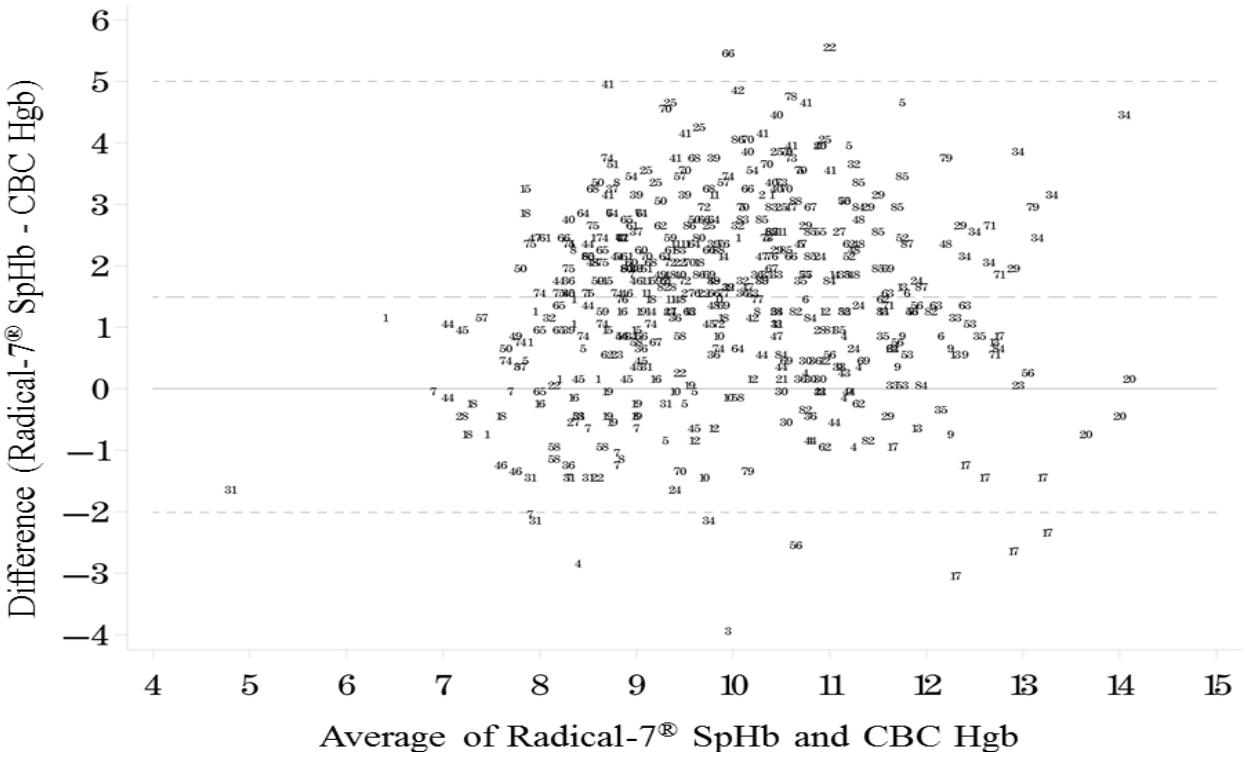
4.0 RESULTS

Eighty-eight patients completed the study between August 2012 and July 2013, with 572 CBC hemoglobin (Hgb) measurements performed (range of 2-15 measurements per patient). Fifty-three of the 88 patients were male (60%), with 84% Caucasian, 15% African-American, and 1% Asian. There were 42 trauma patients (48%) with injuries to spleen (16), liver (10), pelvis (5), kidney (4), vascular (4), lung (2), and heart (1). Twenty-one patients had undergone liver transplant and 11 patients were admitted for gastrointestinal bleeding. Other diagnoses included ischemic bowel (4), hepatic resection (3), pancreas (3), genitourinary (2), retroperitoneal hematoma (1), and necrotizing fasciitis (1). Forty-five percent of the group received at least one unit of red blood cells, 35% received at least one unit of fresh frozen plasma, 27% received at least one unit of platelets, and 14% received at least one unit of cryoprecipitate.

Of the 572 measurements, 86 (15%) were performed while the subject was on vasopressors (norepinephrine and/or vasopressin). Mean SpO2 was 97.6 ± 2.7%, and mean arterial pressure was 78 ± 13.5 mmHg. Radical-7® and iSTAT® Hgb measurements could not be obtained in 88 (15.4%) and 50 (8.7%) of the CBC measurements, respectively. Of the missing Radical-7® measurements, 53/459 (12%) were not able to be obtained in Caucasian patients, while 33/108 (31%) were missing in African-American patients. Bland-Altman

analysis of Radical-7® vs. CBC resulted in an estimated bias of 1.49 g/dL with 95% limits of agreement of -2.0 to 5.0 (SpHb measurement averages 1.49 g/dL higher than CBC Hgb and could be as much as 2.0 g/dL lower or 5.0 g/dL higher than the CBC) (Figure 2). iSTAT® compared to CBC resulted in an estimated bias of -0.63 g/dL with 95% limits of agreement of -3.4 to 2.2 g/dL (Figure 3). Radical-7® compared to iSTAT® resulted in a bias of 2.1 g/dL with 95% limits of agreement of -1.7 to 5.9 g/dL (Figure 4).

Subset analysis comparing SpHb to CBC Hgb was performed examining only points with



PI ≥ 0.5 and PI ≥ 1.00 to eliminate the effect of poor perfusion. This did not improve the overall accuracy of SpHb when compared to CBC Hgb (Table 1). Subset analysis of SpHb was also performed based on ethnicity (Caucasian and African-American groups), patients with jaundice (those with highest bilirubin > 3 mg/dL vs. highest bilirubin ≤ 3 mg/dL), and anemia (CBC Hgb ≤ 8 g/dL vs. CBC Hgb > 8 g/dL). There were no significant changes in accuracy of Radical-7® within these subsets. Results are shown in Table 1.

Radical-7® Hgb showed concordant changes when compared to CBC in 240/400 (60%) of measurements with McNemar statistic of 0.9 (p=0.34). iSTAT® Hgb showed concordant changes when compared to CBC in 330/434 (76%) of measurements with McNemar statistic of 8.65 (p=0.003), indicating statistically significant agreement. Concordance data are shown in Table 2a and b.

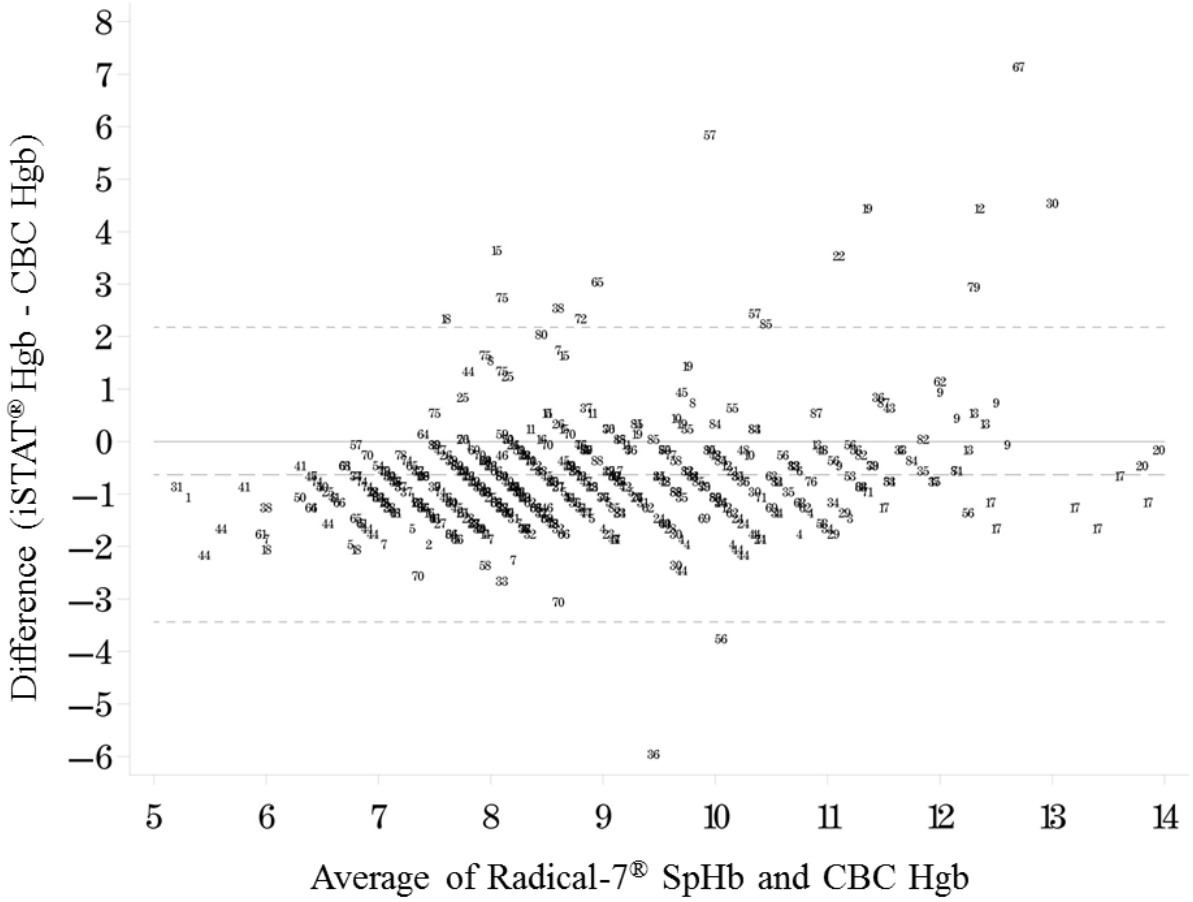


Figure 3. Bland-Altman plot of iSTAT® vs. CBC Hgb measurements.
Numbers indicate patient identification number. Dashed lines represent limits of agreement.

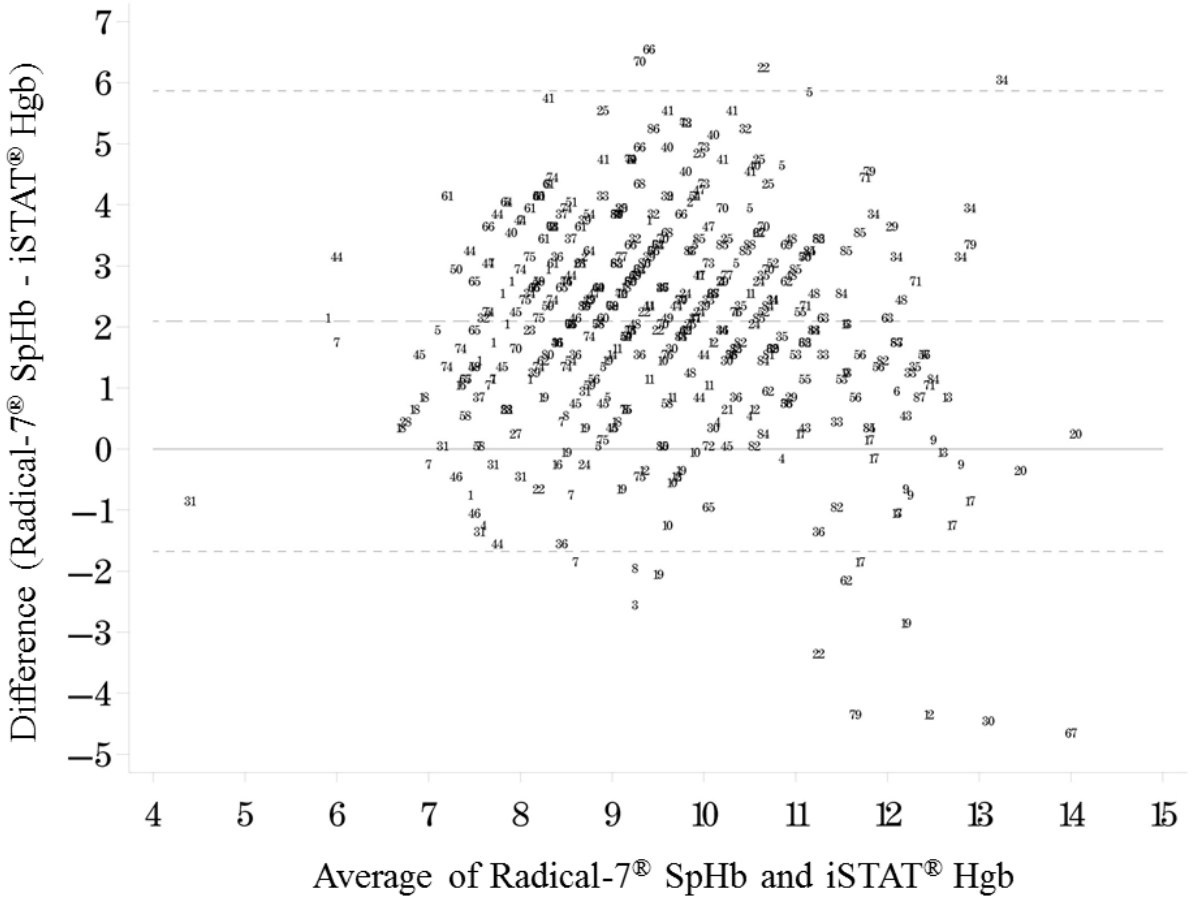


Figure 4. Bland-Altman plot of Radical-7® vs. iSTAT® Hgb measurements.
Numbers indicate patient identification number. Dashed lines represent limits of agreement.

Table 1. Bland-Altman Analysis of Hgb Measurements from Radical-7® vs. CBC, iSTAT® vs. CBC, and Radical-7® vs. iSTAT®

Comparison	Group	Bias	Limits of Agreement	Interval Width	Standard Error
Radical-7® vs. CBC	All measurements	1.49	-2.02, 5.00	7.01	1.28
	PI ≥ 0.5	1.58	-1.73, 4.90	9.90	1.15
	PI ≥ 1.0	1.75	-1.59, 5.10	6.69	1.26
	Caucasian	1.55	-2.01, 5.10	7.02	1.33
	African-American	1.21	-2.09, 4.52	6.61	1.03
	Highest bilirubin > 3	1.38	-2.49, 5.25	7.74	1.41
	Highest bilirubin ≤ 3	1.55	-1.79, 4.89	6.68	1.24
	CBC Hgb ≤ 8	2.14	-0.75, 5.02	5.77	1.28
	CBC Hgb > 8	1.29	-2.02, 4.60	6.62	1.31
iSTAT® vs. CBC	All measurements	-0.63	-3.44, 2.18	5.63	0.63
	Caucasian	-0.58	-3.39, 2.22	5.61	0.65
	African-American	-0.80	-3.62, 2.01	5.63	0.51
	Highest bilirubin > 3	-0.78	-3.44, 1.88	5.32	0.60
	Highest bilirubin ≤ 3	-0.55	-3.43, 2.34	5.77	0.64
	CBC Hgb ≤ 8	-0.44	-2.80, 1.92	4.72	0.86
	CBC Hgb > 8	-0.69	-3.16, 1.78	4.94	0.66
Radical-7® vs. iSTAT®	All measurements	2.09	-1.68, 5.86	7.54	1.32
	PI ≥ 0.5	2.17	-1.50, 5.84	7.64	1.28
	PI ≥ 1.00	2.33	-1.66, 6.32	7.98	1.58
	Caucasian	2.11	-1.79, 6.01	7.80	1.39
	African-American	1.97	-1.14, 5.08	6.22	0.93
	Highest bilirubin > 3	2.18	-1.84, 6.20	8.04	1.48
	Highest bilirubin ≤ 3	2.04	-1.61, 5.70	7.31	1.25
	CBC Hgb ≤ 8	2.57	-0.80, 5.95	6.75	1.46
	CBC Hgb > 8	1.94	-1.71, 5.59	7.30	1.36

Note: Subset analysis was performed on data points with PI ≥ 0.5, PI ≥ 1.00, ethnicity (Caucasian vs. African-American), patients with jaundice (those with highest bilirubin > 3 vs. highest bilirubin ≤ 3), and anemia (CBC Hgb ≤ 8 vs. CBC Hgb > 8). PI provides a relative numeric indication of the pulse strength at the monitoring site.

Table 2a. Concordance Measurements for Radical-7® SpHb vs. CBC Hgb[a]

Change in CBC Hgb	Change in Radical-7® SpHb	
	Decrease	Increase or No Change
Decrease	122 (30.5%)	86 (21.5%)
Increase or no change	74 (18.5%)	118 (29.5%)

[a]McNemar statistic = 0.90 (p=0.34).

Table 2b. Concordance Measurements for iSTAT® vs. CBC Hgb[a]

Change in CBC Hgb	Change in iSTAT® Hgb	
	Decrease	Increase or No Change
Decrease	157 (36.2%)	67 (15.4%)
Increase or no change	37 (8.5%)	173 (39.9%)

[a]McNemar statistic = 8.65 (p=0.003).

5.0 DISCUSSION

Detecting hemorrhage in the critically ill can be difficult based solely on clinical evaluation, and the use of serial hemoglobin measurements is a standard method of monitoring patients at known risk for hemorrhage. However, obtaining these laboratory values requires invasive blood draws which, when repeated, can contribute to iatrogenic ongoing anemia. More importantly, laboratory testing can take significant time, resulting in delays in the recognition and management of acute blood loss.

The development of noninvasive hemoglobin measuring devices can potentially detect hemorrhage rapidly and without requiring a blood draw. This study was designed to evaluate the accuracy of Radical-7® and iSTAT® in measuring hemoglobin when compared to gold standard CBC testing in patients at risk for hemorrhage. In addition, we sought to examine if trends in Radical-7® and iSTAT® measurements correlated with changes in CBC Hgb. Unlike most prior studies that evaluated patients at steady state, this study examines the use of noninvasive hemoglobin monitoring in critically ill patients at significant risk for hemorrhage in which such devices would have direct applicability and benefit over existing standards of care.

The Radical-7® device has been studied in the operating room and in ICU—these studies have had mixed results regarding the accuracy of noninvasive hemoglobin measurements. Prior studies noting the accuracy of the Radical-7® provided some impetus for this study [5,7,11]. Causey et al. examined noninvasive monitoring in surgical and ICU patients, finding mean noninvasive Hgb to be within 0.5 g/dL in both groups [10], and Frasca et al. found even closer correlation (0.0 ± 1.0 g/dL) between Radical-7® measurements and CBC standards [8].

In contrast, however, other studies have found variability that may compromise the clinical utility of noninvasive hemoglobin monitoring [9,12,13,16]. Lamhaut et al. compared the Radical-7® and point-of-care testing to laboratory measurements and found that although bias for both groups did not differ significantly from standard measurements, the precision (defined

as ± 1.0 g/dL) of the Radical-7® was much worse than the point of care device [16]. Gayat et al. noted that SpHb measurements were significantly lower than CBC Hgb, with a mean difference of 1.59 g/dL (95% confidence interval -1.82 to -1.37; $p<0.0001$). Furthermore, SpHb could not be obtained in 8% of patients, particularly older patients with lower diastolic blood pressure, lower CBC hemoglobin, and lower SpO_2 [9]. In a study of patients undergoing pelvic or abdominal surgery, Applegate and colleagues noted that Radical-7® bias increased with blood loss > 1000 mL, hemoglobin less than 9 g/dL, and any intraoperative transfusion, common scenarios in patients at risk for hemorrhage [13].

In this study, the use of the Radical-7® for accurate hemoglobin measurements and temporal trends had significant limitations. We defined accuracy of these methods as within ± 1.0 g/dL of the CBC hemoglobin measurement, a commonly held clinical reference. The bias for Radical-7® measurements was outside of this defined range. More importantly, the Radical-7® had large limits of agreement, indicating a high degree of variability in the precision of this device.

Although the Radical-7® device is reported to be affected by low arterial perfusion, low oxygen saturation, high bilirubin, and severe anemia, specific definitions of these conditions have not been delineated. In this study, subset analysis eliminating patients with clinical jaundice (bilirubin > 3) did not improve the accuracy of SpHb. It should be noted, however, that this subset analysis utilized all measurements from patients with highest bilirubin > 3, as concomitant bilirubin measurements were not performed for all hemoglobin measurements. SpHb measurements may not be as accurate in patients with severe anemia. In this study, subset analysis evaluating Radical-7® SpHb measurements with concomitant CBC Hgb > 8 did reveal a decreased bias in the noninvasive measurements; however, the bias (1.3 g/dL) still fell outside our definition of accuracy. The definition of anemia in the ICU has evolved over the last decade, with guidelines suggesting that in many patients, transfusions may be delayed until hemoglobin values fall below 7 g/dL without increased mortality [17,18]. As such, many critically ill patients may be maintained with hemoglobin between 7 g/dL and 8 g/dL, and the utility of devices that cannot monitor hemoglobin accurately in this range may be limited.

Similar to the Gayat study, in our patient population, SpHb was unable to be obtained in 15% of time points. In this study, there were no significant differences in mean arterial pressure and oxygen saturation when SpHb was unable to be obtained when compared to time points where SpHb was able to be measured. Missing data was more likely to occur in African-American patients (31%) when compared to Caucasian patients (12%).

Frequently, the trend in serial hemoglobin measurements, rather than absolute hemoglobin level, is often used to evaluate ongoing hemorrhage or clinical response to transfusion. We examined the concordance of changes in serial Radical-7® and iSTAT® Hgb measurements to the CBC Hgb measurements. In this study, SpHb was only concordant with changes in CBC Hgb 60% of the time, making it difficult to predict ongoing blood loss using the trends of noninvasive hemoglobin measurements.

In contrast, hemoglobin measurements using the iSTAT® device were more accurate than those obtained with Radical-7®. iSTAT® Hgb bias fell within ± 1.0 g/dL of the CBC Hgb, meeting the definition of accuracy in this study. iSTAT® limits of agreement still demonstrated a large interval (-3.4 to 2.2); however, this was significantly less than limits for SpHb (-2.0 to 5.0). Furthermore, concordance data suggested that serial measurements of iSTAT® Hgb agreed with CBC trends more frequently than SpHb as well.

There are some limitations to this study. The definition of accuracy (± 1.0 g/dL) may be somewhat arbitrary, although it has been utilized in other studies [13,19]. In addition, a frequently utilized clinical rule of thumb is that a decrease in hemoglobin by 1.0 g/dL roughly corresponds to the loss of one unit of blood. However, the relevance of a measurement error of this magnitude may need to be taken in context of the actual hemoglobin; a 1.0 g/dL variability at a hemoglobin of 14 g/dL carries a different clinical connotation than a 1.0 g/dL variability at a hemoglobin of 8.0 g/dL. In our study, CBC Hgb was less than 8.0 g/dL in 23% of measurements, where the Radical-7® may be less accurate. Although some may argue that transfusion decisions in patients with low baseline hemoglobin may be based on clinical, rather than laboratory, data, it is frequently in the acutely anemic patient where measured data may be most useful. Finally, almost half of the patients in this study received blood transfusions. It is possible that post-transfusion blood sampling was performed prior to complete intravascular equilibration and that regional tissue perfusion and noninvasive tissue hemoglobin measurements may be affected by fluid redistribution in a different manner than intravascular hemoglobin.

6.0 CONCLUSION

Radical-7 ® SpHb was inaccurate when compared to CBC Hgb levels, and serial SpHb achieved concordance with CBC Hgb 60% of the time. As such, the clinical utility of Radical-7® as a rapid, noninvasive predictor of acute hemorrhage may be limited.

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LIST OF ABBREVIATIONS AND ACRONYMS

CBC	complete blood count
Hgb	hemoglobin
ICU	intensive care unit
PI	perfusion index
SpHb	continuous hemoglobin measurement
SpO_2	arterial oxygen saturation